

Protocol for a phase III randomised trial of image-guided intensity modulated radiotherapy (IG-IMRT) and conventional radiotherapy for late small bowel toxicity reduction after postoperative adjuvant radiation in Ca cervix

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ABSTRACT

Introduction: External beam radiation followed by vaginal brachytherapy (±chemotherapy) leads to reduction in the risk of local recurrence and improves progression-free survival in patients with adverse risk factors following Wertheim's hysterectomy albeit at the risk of late bowel toxicity. Intensity Modulated Radiotherapy (IMRT) results in reduction in bowel doses and has potential to reduce late morbidity, however, needs to be confirmed prospectively in a randomised trial. The present randomised trial tests reduction if any in late small bowel toxicity with the use of IMRT in postoperative setting.

Methods and analysis: Patients more than 18 years of age who need adjuvant (chemo) radiation will be eligible. Patients with residual pelvic or para-aortic nodal disease, history of multiple abdominal surgeries or any other medical bowel condition will be excluded. The trial will randomise patients into standard radiation or IMRT. The primary aim is to compare differences in late grades II–IV bowel toxicity between the two arms. The secondary aims of the study focus on evaluating correlation of dose–volume parameters and late toxicity and quality of life. The trial is planned as a multicentre randomised study. The trial is designed to detect a 13% difference in late grades II–IV bowel toxicity with an α of 0.05 and β of 0.80. A total of 240 patients will be required to demonstrate the aforesaid difference.

Ethics and dissemination: The trial is approved by institutional ethics review board and will be routinely monitored as per standard guidelines. The study results will be disseminated via peer reviewed scientific journals, conference presentations and submission to regulatory authorities.

Registration: The trial is registered with clinicaltrials.gov (NCT 01279135).

ARTICLE SUMMARY

Article focus

- Does the use of Intensity Modulated Radiotherapy (IMRT) lead to reduction in late toxicity in women receiving postoperative adjuvant radiation for cervical cancer?
- Can the dose volume parameters for late bowel toxicity be prospectively predicted?
- Is there a difference in late quality of life of patients undergoing standard radiation or IMRT for postoperative adjuvant radiation for cervical cancer?

Key messages

- The study is designed to test the superiority if any of advanced radiation delivery techniques in reducing late morbidity of adjuvant pelvic radiation in women with cervical cancer.
- The results of the study may redefine standard of care of adjuvant treatment techniques for cervical cancer.

Strengths and limitations of this study

- Phase III randomised multicentric study.
- Primary end-point focuses towards late morbidity scoring.

INTRODUCTION

Randomised trials conducted in the 1990s by the GOG group established adjuvant radiation and/or chemotherapy as standard of care in patients with intermediate or high-risk factors.^{1–3} However, surgical extirpation of uterus, postoperative adhesions of bowel loop in pelvis and altered microvasculature

increase vulnerability of small bowel to the adverse effects of pelvic irradiation. Two large trials of adjuvant radiation reported upto 58% incidence of acute grade II gastrointestinal toxicity and upto 10% incidence of grades III–IV toxicity following external beam radiation which increases further with the addition of chemotherapy or vaginal brachytherapy.⁴ More contemporary series using pelvic radiotherapy in combination with brachytherapy have reported 80–90% incidence of acute grade II gastrointestinal toxicity. A retrospective study of late toxicity among patients treated with adjuvant pelvic radiotherapy along with vaginal cuff brachytherapy reported 16.4% incidence of late grades II–IV small bowel toxicity and upto 20.3% incidence of late rectal grades I–II toxicity. Pelvic dose of >54 Gy and age >60 years were identified as risk factors for late bowel toxicity.⁵ Clinically meaningful data regarding small bowel complications can also be derived from studies of postoperative radiation for rectal cancer. Long-term follow-up of Uppasla trial reported 6% incidence of small bowel obstruction after surgery alone and 11% after postoperative radiation.⁶ An overview undertaken by Kavanagh *et al*⁷ reported incidence of late small bowel perforation of the order of 2–9% with 50 Gy of pelvic radiotherapy. However, the risk may be increased in those undergoing postoperative radiation or receiving brachytherapy and concurrent chemotherapy.

Bowel sequelae can, however, be potentially reduced by decreasing the dose to the small bowel. Baglan *et al* have demonstrated significant correlation between acute grade III bowel toxicity and volume of bowel receiving 15 Gy (V₁₅) in patients with rectal cancer. While patients with grade III toxicity had V₁₅ of 319 cc, those without grade III toxicity had a mean V₁₅ of 127 cc.⁸ These dose–volume parameters were validated in a separate cohort by Robertson *et al*⁹ and a cut-off of V₁₅ at 150 cc was proposed to be predictive of acute grade III toxicity. However, these cut-off's may vary depending on the method of delineation of small bowel (ie, individual bowel loops vs whole peritoneal cavity). Only one study has investigated correlation of small bowel dose–volume parameters with late toxicity. Patients receiving three-field radiotherapy (RT) with estimated 165 cc of small bowel within the pelvic field had a 6% incidence of bowel toxicity as compared with 37% in those receiving radiation with parallel opposed portal and estimated 790 cc of bowel within the pelvic field. The authors modelled complication risk as a power law and predicted iso-toxicity for each doubling of the volume of bowel in the field if the RT dose was reduced by 17%.¹⁰

Intensity Modulated Radiotherapy (IMRT) reduces the small bowel dose by 50–67% as compared with conventional whole pelvis radiotherapy. Prospective studies evaluating IMRT have demonstrated 30% reduction in acute grade II toxicity and upto 30% reduction in the prescription of antidiarrhoeals.^{11 12} A lower incidence of 15% has been noted within IMRT series wherein only pelvic IMRT (without brachytherapy) has been used. Schwarz *et al*¹³ recently reported on their experience with

pelvic IMRT and intravaginal brachytherapy and have reported 35% incidence of grades II–III acute toxicity. In patients undergoing combination of external radiation and brachytherapy the use of IMRT is associated with decreased incidence of grade II or higher bowel toxicity.¹⁴ In a recent study, Vandecasteele *et al*¹⁵ have demonstrated that the use of Intensity Modulated Arc Therapy is associated with reduced late grade II gastrointestinal toxicity of 4%. However, no incidence of grades III/IV toxicity was observed. Though phase II studies have reported favourable outcomes with the use of IMRT there are no randomised studies comparing radiation and IMRT for bowel toxicity. The present randomised controlled trial investigates difference in late grades II–IV bowel toxicity between standard conformal box field radiation and pelvic IMRT.

HYPOTHESIS

Preliminary results of phase II studies of IMRT suggest that postoperative pelvic IMRT is associated with reduced acute toxicity. On the basis of observed differences in acute toxicity with IMRT we hypothesised that ‘The use of image guided intensity modulated radiation therapy (IG-IMRT) will lead to clinically and statistically significant reduction in late grades II–IV bowel morbidity after adjuvant pelvic radiation’.

METHODS AND ANALYSIS

Study design

The study is a phase III open, parallel group randomised controlled trial designed to test the efficacy of IG-IMRT against standard radiation in reducing late bowel grades II–IV toxicity. The study will follow permuted block stratified randomisation wherein the study population will be randomised to receive standard radiation or IG-IMRT. Patients will be stratified according to type of surgery (Wertheim's hysterectomy or simple hysterectomy) and use of chemotherapy (adjuvant chemoradiation or radiation alone). All randomisation will be done centrally through Epidemiology and Clinical Trials Unit at Advanced Centre for Treatment Research and Education in Cancer (ACTREC).

Study aims

The primary aim of the randomised trial is to evaluate differences in late grades II–IV bowel toxicity in the standard radiation and IG-IMRT arms. The secondary and tertiary aims will focus on investigating correlation between dose–volume histogram parameters and clinical occurrence of grades II–IV bowel toxicity and differences if any in quality of life (QOL) between the two arms.

The study also has a preoperative translational imaging arm that focuses on obtaining multiparametric MRI and positron emission tomography to identify pre-operative quantitative functional imaging factors that predict for local recurrence. The preoperative imaging arm however is not open for multicentric study.

Research setting

The study will be conducted at Advanced Centre for Treatment Research and Education in Cancer and Tata Memorial Hospital, Tata Memorial Centre, Mumbai and other collaborating centres within India.

Participants and research eligibility

Patients more than 18 years of age, who have undergone simple or Wertheim's hysterectomy for early cervical cancer (Stage IB1-IIA) and require postoperative adjuvant radiation or chemoradiation either due to adverse histopathological factors or suboptimal lymph nodal dissection, will be eligible for study inclusion. Patients with suspicious gross pelvic nodal disease on postoperative imaging need to undergo nodal fine needle aspiration or biopsy to confirm absence of gross nodal disease.

Exclusion criteriae

Patients with para-aortic nodal disease, history of multiple abdominal surgeries or any other medical conditions placing patient at risk of high baseline gastrointestinal toxicity will be excluded. Those with previous history of radiation to the abdomen or pelvis will also be excluded.

STUDY PROCEDURES

Once included in the study following will be study-related procedures.

Patient preparation and treatment simulation

The patient preparation procedures will remain uniform and will not be dependent on arm allocation.

Vault marker placement

Prior to treatment planning all patients will undergo silver marker placement in the vaginal vault. A total of 2–3 silver markers will be inserted to facilitate identification of cranial limit of vaginal vault on planning CT scan. Radiation planning scan will be obtained with empty and full bladder. All patients will be prescribed prophylactic antibiotics to prevent urinary tract infection after marker placement.

Empty bladder scan

For the empty bladder scan patients will be asked to empty the bladder. Patients will be positioned supine with arms above the head. Three radio-opaque markers will be placed at laser intersection points on lower abdomen. A radio-opaque marker will be placed at the introitus while obtaining the scan. CT scan will then be obtained from L3/4 junction to midthigh at an inter-slice thickness of 3 mm.

Full bladder scan

Full bladder scan will be obtained with full bladder after injecting intravenous contrast. Patients will be instructed to consume 500 ml of water and wait for 30 min.

Patients will be positioned supine as during empty bladder scan and 3 mm CT slices will be obtained from diaphragm to mid-thigh after injecting 80–100 ml of intravenous contrast. No oral contrast is administered at this time.

Contouring

As differences in target delineation and field shaping between the standard and IG-IMRT arms could possibly lead to bias in evaluation of toxicity hence all target and organ at risk (OAR) delineation is done prior to randomisation. All images will be transferred from imaging workstation to treatment planning workstation. While full bladder scan will be the primary dataset, the empty bladder scan will serve as the secondary data set. A bony registration will be performed between two image sets for purpose of contouring and radiation planning.

The following structures will be contoured: Vagina Empty Bladder (V_EB). This will include upper half of vagina on empty bladder scan. Vagina Full Bladder (V_FB): upper half of vagina on full bladder scan. Clinical Target Volume (CTV) will be contoured on both empty and full bladder scan. The cranial limit of CTV Full Bladder (CTV_FB) and CTV Empty Bladder (CTV_EB) will extend 1 cm superior to visualised vault. CTV in either case will extend medial to pelvic muscles and inferiorly to half of vaginal length. The CTV will be expanded 1–1.5 cm anteriorly and will not be edited from bladder and small bowel. The posterior extent of CTV extends upto the mesorectal fascia. Internal Target Volume (ITV) will be generated by performing union of CTV_EB and CTV_FB. ITV will be expanded by another 7 mm to generate Planned Target Volume (PTV) Primary (PTV_P). CTV nodes (CTV_N) will be delineated through 7 mm circumferentially expansion of pelvic vessels (Common Iliac Nodes (Upper Extent of vessels L5-S1 Interface+External+Internal Iliac+Presacral+Obturator Lymph Nodes) however edited along muscles and bones. CTV_N will be symmetrically expanded by 5 mm to obtain PTV_N. PTV_P and PTV_N will be merged to generate PTV 50 Gy; OAR) delineation would include urinary bladder, rectum, sigmoid, large bowel and small bowel (individual loops), pelvis, head of femur and both kidneys. Bowel will be uniformly contoured 2 cm cranial to PTV 50 Gy as individual loops.

Radiation planning (standard arm)

Patients randomised to conventional radiotherapy arm will receive radiotherapy with megavoltage radiation through conformal four-field box technique. Investigators have the options of using blocks or multileaf collimators for field shaping. The field should conform to the PTV 50 Gy contours with 7 mm margin for multileaf collimator leaves/blocks. In all cases 95% of PTV_50 Gy should receive 95% of the prescription dose and volume of hotspots (107%) should be minimised inside and outside the PTV. Differential beam weighting is permitted to reduce hot spots within and outside the PTV and reduce OAR dose as feasible.

Radiation planning (IMRT arm)

Empty and full bladder scans are obtained for ITV generation. All planning will be done on full bladder scans only. For IMRT planning following are the dose volume recommendations.

PTV 50 Gy: 95% of PTV should receive 95% of the prescription dose; small bowel doses should be reduced as low as possible. All attempts should be made to keep V15<190 cc. In addition V40 Gy should be no more than 100 cc. Less than 60% of rectal volume should receive >/=30 Gy and less than 35% of bladder should receive >/=45 Gy; Less than 15% of the femoral Head should receive 30 Gy.

A total of 50 Gy/25 fractions will be prescribed to primary and nodal PTV and will be delivered over 5 weeks.

Daily radiation treatment

Irrespective of the arm allocation patients will be treated with full bladder. All patients will be instructed to consume 500 ml of water 30 min prior to the radiation procedure. In the IG-IMRT arm daily pretreatment imaging will be mandatory. Those in the standard EBRT arm should undergo weekly electronic portal imaging/simulator check film.

Chemotherapy

Whenever indicated, patients will receive concurrent platinum-based chemotherapy. For those with creatinine clearance >50 ml/min cisplatin will be administered at a dose of 40 mg/m² weekly during external beam radiation. In case of creatinine clearance between 40 and 50 ml/min a 20–25% dose reduction may be applied. Patients with creatinine clearance of less than 40 will be treated with radiation alone. Assessment of creatinine clearance will be done prior to each cycle of chemotherapy.

Brachytherapy

All patients included in the study will receive vaginal cylinder-based brachytherapy after completing external radiation. The target volume for brachytherapy will include upper one-third of vagina. All patients will receive 2 fractions of 6 Gy high-dose rate brachytherapy prescribed to 0.5 cm from the vaginal cylinder surface. These will be delivered 1-week apart. All brachytherapy will be executed using CT-based planning.

On treatment evaluation

All patients will be required to complete CTCAE scoring and QOL assessment (EORTC QLQC30 and Cx-24) prior to initiating adjuvant radiation. While on treatment all patients will be seen by a radiation oncologist weekly and acute toxicity will be documented using CTCAE V3.0. At treatment conclusion a repeat evaluation of QOL will be done.

Follow-up

Patients will be scheduled for follow-up every 3 monthly for the first 2 years and 6 monthly thereafter. At each follow-up a systemic and local examination will be performed. CTCAE and EORTC QLQC-30 and Cervix-24 forms will also be filled. Patients will undergo radiological investigations (CT abdomen/pelvis and chest x-ray) on an annual basis. However, symptom directed investigations may be undertaken at any time point.

STATISTICAL CONSIDERATIONS

Primary end point

The study sample size is calculated towards primary end point. To demonstrate 13% reduction in proportion of late grades II–IV bowel toxicity (from 18% to 5%) with two-sided $\alpha=0.05$ and power of 0.80, a total of 218 patients will be required (109 in each arm). Accounting for 10% attrition a sample size of 240 will be needed. Trial results towards the primary end point will be reported at a median follow-up of 3 years. All analyses will consider the worst gastrointestinal toxicity grade during follow-up for statistical analyses. Clinically significant toxicities of other organs will be reported, however, will not be used for study analyses. An interim analysis is planned when 50% of the accrued patients complete 18 months of follow-up.

Stopping rules

At interim analysis if absolute incidence of late grades II–IV toxicity in the standard arm exceeds 25% more than the investigational arm than data and safety monitoring committee of the institutional review board will be approached for review and decision regarding early closure of the clinical trial. However, if the observed difference is less than 25% than a p value of 0.025 will be used to reject the null hypothesis. The p value is adjusted as per Bonferroni's correction to account for multiple looks at the same data.

Data collection

All trial data will be maintained by the principal investigator of the study at ACTREC, Tata Memorial Centre, Mumbai, India.

Treatment planning data

The mean, median and maximum dose of PTV, bladder, rectum, sigmoid, large bowel, small bowel and pelvis will be reported. In addition, volume of small bowel and large bowel will be recorded for each patient. In addition absolute volume of small bowel and large bowel receiving 15, 30, 40 and 50 Gy (V15, V30, V40 and V50) will be recorded.

Treatment data

Records of treatment will be summarised to report the total radiation dose, brachytherapy dose, chemotherapy

cycles, overall treatment time, breaks if any in radiation treatment.

Toxicity evaluation

Toxicity will be reported using CTCAE V.3.0. CTCAE forms will be filled before starting radiation, weekly during radiation treatment and on each scheduled follow-up. If any toxicity occurs at another time point additional forms will be filled to capture the same.

Quality of life

EORTC QLQC30 and Cx-24 modules will be used for evaluating QOL of patients. All patients will undergo QOL evaluation at baseline, after treatment and at each subsequent follow-up.

Clinical outcome data

In addition the study will also record status of disease at each follow-up. A record of local examination findings will be kept. Systemic work-up will be performed only once a year and status of regional and distant control will be reported accordingly.

Quality control

Protocol compliance

Inability to receive the entire planned treatment (standard or IG-IMRT) will be considered as a major violation. Similarly, inability to receive the entire planned chemotherapy will be considered as major violation. However, if patient misses less than 2–3 fractions of radiation or upto two cycles of chemotherapy then it will be considered as minor violation. Inability to achieve PTV coverage with 95% isodose or inability to meet small bowel constraints (V15, V40) will be considered as minor violation. However, other prescribed constraints are soft constraints and inability to achieve them will not amount to violation.

Event reporting

All events will be captured with CTCAE V.3.0 and all serious adverse events will be notified to institutional review board within seven working days and all deaths within 24 h of occurrence.

Trial monitoring

The trial will be monitored at a regular interval by the institutional data and safety monitoring board and its report will be submitted to the ethics committee and institutional review board.

DATA ANALYSIS PLAN

Primary aim

The study data will be analysed for the primary aim. The overall proportion of patients in standard and intervention arm developing late grades II–IV bowel toxicity will be calculated using Fisher's exact test. Furthermore, the proportions will be compared within the planned

stratifications. A p value of <0.025 and <0.05 will be used to reject the null hypothesis at interim and final analyses, respectively.

Secondary aim

Dose–volume correlation

Dose–volume data for bowel will be categorised to calculate volume of bowel receiving 15, 30, 40 and 50 Gy and its ability to predict late grades II–V toxicity will be evaluated. Maximum grade of bowel toxicity across all subscales of CTCAE V.3.0 will be calculated. The sensitivity and specificity of various bowel volume indices in predicting grades II–IV toxicity will be calculated with receiver operator characteristics curve. All data will be dichotomised across identified cut-off values. The statistical validity of bowel dose–volume cut-off's in predicting grade II or higher toxicity will be evaluated by Fisher's exact test.

QOL analysis

Standard recommendations of EORTC will be used to analyse QOL data of the two study arms.

Implications for research

The proposed study seeks to study impact of IG-IMRT in late morbidity reduction in one of the commonest cancers in women in developing countries. If this study demonstrates reduction in late morbidity with IG-IMRT than it would redefine standards for adjuvant radiation in cervical cancer.

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Contributors SC participated in project concept, design, manuscript preparation and approval, Principal Investigator for Multicentre Trial. RE participated in design of study protocol, manuscript draft review and approval of final content. UM participated in design of study protocol, manuscript draft review and approval of final content. SM participated in substantial contribution to acquisition of data, manuscript preparation, final approval. RP participated in conceptual design, manuscript preparation, final approval (Medical Physics Part), SNP participated in conceptual design, manuscript preparation, final approval (Medical Physics Part), SK participated in

conceptual design, manuscript draft, final approval of version (Statistics Part), RK participated in conceptual design, revising project for intellectual content and final approval of draft. AM participated in analysis and interpretation of data, manuscript review and final approval of draft. TSS participated in acquisition of data, manuscript review and final approval of manuscript draft. JG participated in data acquisition, revising project for intellectual content and final approval of draft. SG participated in data acquisition, revising project for intellectual content and final approval of draft. BT participated in acquisition of data, manuscript review and final approval. ShaS participated in principal investigator, collaborating site, substantial contribution to data acquisition, revising article and final approval. SaS participated in principal investigator, collaborating Site, substantial contribution to data acquisition, revising article and final approval. SCH participated in principal investigator, collaborating site, substantial contribution to data acquisition, revising article and final approval. SKS participated in project concept, design, execution, manuscript preparation and approval and principal investigator.

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Ethics approval Memorial Centre Ethics Review Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Reader can access extra data (individual patient data) through the principal investigator (SC) at supriyasastri@gmail.com.

REFERENCES

1. Rotman M, Sedlis A, Piedmonte MR, et al. A phase III randomized trial of postoperative pelvic irradiation in stage IB cervical carcinoma with poor prognostic features: follow-up of a gynecologic oncology group study. *Int J of Radiat Oncol Biol and Phys* 2006;65:169–76.
2. Peters WA III, Liu PY, Barrett RJ II, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol* 2000;18:1606–13.
3. Sedlis A, Bundy BN, Rotman MZ, et al. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage Ia carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a gynecologic oncology group study. *Gynecol Oncol* 1999;73:177–83.
4. Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol* 2004;92:744–51.
5. Chen S-W, Liang JA, Yang SN, et al. Radiation injury to intestine following hysterectomy and adjuvant radiotherapy for cervical cancer. *Gynecol Oncol* 2004;95:208–14.
6. Frykholm GJ, Glimelius B, Pahlman L. Preoperative or postoperative irradiation in adenocarcinoma of the rectum: final treatment results of a randomized trial and an evaluation of late secondary effects. *Dis Colon Rectum* 1993;36:564–72.
7. Kavanagh BD, Pan CC, Dawson LA, et al. Radiation dose volume effects in the stomach and small bowel. *Int J Radiat Oncol Biol Phys* 2010;76:S101–7.
8. Baglan KL, Frazier RC, Yan D, et al. The dose-volume relationship of acute small bowel toxicity from concurrent 5-FU-based chemotherapy and radiation therapy for rectal cancer. *Int J Radiat Oncol Biol Phys* 2002;52:176–83.
9. Robertson JM, Lockman D, Yan D, et al. The dose volume relationship of small bowel irradiation and acute grade III diarrhoea during radiotherapy for rectal cancer. *Int J Radiat Oncol Biol Phys* 2007;69:732–9.
10. Letschert JG, Lebesque JV, deBoer RW, et al. Dose-volume correlation in radiation-related late small-bowel complications: a clinical study. *Radiother Oncol* 1990;18:307–20.
11. Mundt AJ, Roeske JC. Can intensity-modulated radiation therapy replace brachytherapy in the management of cervical cancer? Counterpoint. *Brachytherapy* 2002;1:192–4.
12. Portelance L, Winter K, Jhingran A, et al. Post-operative pelvic intensity modulated radiation therapy (IMRT) with chemotherapy for patients with cervical carcinoma/RTOG 0418 phase II study. *Int J Radiat Oncol Biol Phys* 2009;75:S640–1.
13. Schwarz JK, Wahab S, Grigsby PW. Prospective phase I/II trial of helical tomotherapy with or without chemotherapy for postoperative cervical cancer patients. *Int J Radiat Oncol Biol Phys* 2009;81:1258–63.
14. Kabarriti R, Thawani N, Gao W, et al. Feasibility and acute toxicity of intensity modulated radiation therapy with CDDP chemotherapy for postoperative pelvic radiation in patients with cervical cancer. *Int J Radiat Oncol Biol Phys* 2009;75:S376–7.
15. Vandecasteele K, Tummers P, Makar A, et al. Postoperative intensity modulated arc therapy for cervical and endometrial cancers: a prospective report on toxicity. *Int J Radiat Oncol Biol Phys* 2012;84:408–14.